LOST IN TRANSLATION: THE SCIENTIST'S PERSPECTIVE IN NAVIGATING FROM PIPET TO PATIENT

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ABSTRACT

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Translational Research (TR) is defined as the systematic effort to convert basic research knowledge into practical applications to enhance human health. This thesis explores the current state of translational research, and uses the perspectives of research scientists involved in TR to gain insight into the barriers that systematically inhibit translational progress. To explore such perspectives, I compiled personal commentaries and narratives to delineate the cultural, institutional, and political shifts that must occur to encourage successful implementation. A few specific themes emerged in regards to the significant barriers in translational research: barriers established by scientific culture, and barriers caused by research infrastructure. Analyzing these themes under the current translational research structure led me to understand that training a new breed of collaborative researchers is necessary. Doing so not only requires an infrastructure capable of providing a nurturing environment, but also the support and understanding of why this change is imperative. Successful translational research in today's scientific landscape requires a paradigm shift in training and career development, which will lay the foundation for improvements in research effectiveness and patient outcomes.

INTRODUCTION

How long does it take for a scientific discovery to help a patient affected with disease? Hofstadter's Law famously states, "It always takes longer than you expect, even when you take into account Hofstadter's law." It has been well known that a novel drug, medical device or other intervention currently can take about 14 years and cost $2 billion or more to develop, with a rate of failure at clinical trials exceeding 95% (National Center for Advancing Translational Sciences, 2015). When considering the costs of bringing a relevant scientific finding to the market as a therapeutic intervention suitable for public use, not only must we acknowledge Hofstadter's Law in regards to the length of time the process will take, but also that it will be far harder and much more puzzling than initially predicted. This circular and confounding scheme suitably describes the current state of Translational Research.

Medical and scientific advancements resulting from the explosion of technological innovation in the past few years have created a new problem: how to effectively integrate new discoveries into clinical practice. Translation is the process of turning observations in the laboratory, clinic, and community into interventions that improve the health of individuals and the public. As a concept designed for the medical world, Translational Research (TR) emerged in response to growing concern over the long time lag between scientific discoveries and widespread changes in treatments, practices, and common understandings.

TR is defined as the systematic effort to convert basic research knowledge into practical applications to enhance human health in the forms of diagnostics, therapeutics, medical procedures, and public health interventions. The enterprise covers all areas of science, from biological to physical to social. Essentially any effort to create public benefit from studies utilizing the scientific method fit into this category.

The umbrella of translational research covers various subcategories related to specialized fields such as biology, physical sciences, genetics, epidemiology, social sciences, etc. With such a broad spectrum of topics and parties involved, improving the Translational Research process is complex and intimidating, occasionally causing scientists to avoid associating with collaborative efforts in favor of personal initiatives to streamline their own research. Though many scientists recognize the need for improvements in translational efficacy, responsibility diffuses across every involved party, and one individual or group's efforts to speed up implementation may isolate them from the collaborative initiatives that encourage translation.

Terminology matters. Collaboration among scientists is successful insofar as the parties involved communicate effectively and share common definitions of the goals they are working toward. Since TR spans many fields and can be used to iterate various research elements, much of the language is used inexactly, with varying connotations and interpretations. Moreover, there are distinct yet overlapping perspectives from which to view the process of translation. For example, translating a mechanistic discovery into a therapeutic drug involves clinical trial considerations and 10-year time frames. On the other hand, translating a biomedical device requires mechanical testing and oversight, with a pre-clinical time frame of up to 10-years, and translating a genetic analysis into a public health policy requires overcoming political hurdles that involve additional trained specialists, with much faster time frames.

The terminology can be confusing in biological and medical studies, especially those impacting patients and the clinic that are not directly involved in the process. These parties may lose sight of some of the subtleties involved in the process, propagating any complex roadblocks and making it difficult to implement strategies that ease the process. Some concepts are often used erroneously, relegating "basic" to

all laboratory work and "applied" to clinical studies, with translation being a unidirectional arrow from bench to bedside. However, these descriptions misconstrue the fundamental meaning of the terminology and lead to a poor understanding of the iterations that occur during the process. Accurate descriptions are necessary for translational progress. Since the goals of translation revolve around collaboration of various fields, there should be no ambiguity among those collaborators as to the goal they are working toward.

As the goals of Translational Research have disseminated through the scientific world, a variety of translational models have been proposed. Translation has been described as a "bench to bedside" model (Wolf, 1974), a two-phase process (Sung, 2003), a continuum with five T-phases (T0-T4) (Khoury, 2007), and a process of three translational (3T's) phases (Dougherty, 2008). It could perhaps be argued that translational research is merely a re-packaging of the term "applied research," which has been in the lexicon for over fifty years. The term has also been used to refer to the relevance of basic science to public health practice.

In order to determine the best approach to the process of translational research, we must understand the struggles perceived by scientists involved. Ironically, given all the discourse about translational science, scant attention has been paid to the voices of those at the start of the pipeline, those whose basic research work is being "translated." In this study I want to highlight the voices of the scientists involved in translational pathways. The intent, support, motivation, and public reception of the scientist are oftentimes the most important factors that drive a project from a culture tube to an IV bag. The scientist also is the sole agent ultimately responsible for pursuing a project past initial publication. With this thesis, I reviewed the roles and perspectives of researchers with respect to translational goals, to outline the challenges that exist and the most

effective efforts to overcome such challenges. As I came to understand the perspectives of the researchers involved in the translation of a discovery to clinical practice, I realized that the process of translation is not inherently flawed, and can be restructured around the interests of the researchers to improve efficiency.

GOALS OF THIS THESIS

This thesis explores the current state of translational research, and generalizes factors that influence the feasibility of implementation, in order to suggest systematic or institutional improvements. Incorporating perspectives of research scientists that have attempted to carry a research project into clinical application provided insight into the barriers that systematically inhibit researchers' translational progress. To explore these perspectives, I compiled personal commentaries to delineate the cultural, institutional, and political shifts that must occur to encourage successful implementation.

From my findings, a few specific themes emerged in regards to the significant barriers in translational research. I compiled the perspectives into two main themes: commentaries on the barrier of culture and collaboration, and on the barrier of funding and infrastructure. Almost all involved participants saw translational hindrance as primarily cultural, resulting in a need for collaborative innovators in medicine and the need for extensive communication among all involved parties. Analyzing these themes under the current translational research structure led me to understand that training a new breed of collaborative researchers is necessary. Doing so not only requires an infrastructure capable of providing a favorable environment, but also the support and understanding of why this change is imperative. Traditional training schemes continue to promote communication silos in both the basic scientific and clinical realms. These walls must be broken down to create the next wave of translational researchers.

Already, translational research programs in the basic sciences are evolving out of the traditional schemes. From the clinical standpoint, more focus and institutional support must be given to attract physicians to engage in research previously thought to have no place in clinical work. Alternatively, there need to be pathways for scientists to engage the clinic to truly understand the disease they are trying to impact. Successful translational research in today's scientific landscape requires a paradigm shift in training and career development, which will lay the foundation for improvements in research effectiveness and patient outcomes.

METHODS

To comprehend the successes and pitfalls of current translational initiatives, I used peer-reviewed sources to identify specific cases of translational successes. In each case, I analyzed the researcher's perspective of the process of implementation, using firsthand accounts and interviews. Various contexts for translational research emerged in the scientific literature, allowing me to compare perspectives across multiple disciplines. Comparing these studies highlighted a few themes that appeared in the opinions of translational researchers, allowing me to identify specific common barriers to translation. The importance of this work is inherent in the natural conclusions that followed. The themes of collaboration's necessity led to conclusions that can drive policies and initiatives necessary to ease the processes of translation and implementation, starting with the most important party: the researcher. I focused on the biomedical scientific literature of pharmaceuticals, devices, and genomics because it illustrates how those most directly involved in doing Translational Research interpret the label of TR.

BACKGROUND

Bench to Bedside: what is the need for translational research?

How many diseases do we now know the exact molecular basis? Turns out it's exactly 4993 (OMIM), which is amazing, especially considering most molecular discoveries have occurred in the last 30 years. In terms of knowledge, this clearly makes the world much better off than before. But in terms of health, how many of those 4993 diseases now have treatments available? As it turns out, only about 250 discoveries of disease mechanisms have led to treatment (TEDMED, 2012). There is now a gap emerging between what we know and what can be applied to patients, growing wider with each biomedical discovery that can't be directly implemented. The problem of implementation is subtly inherent in the scientific research conducted, but involves the complex interaction of various research and non-research groups. Implementation refers to the ability to take some fundamental information that basic biology teaches about the causes of disease, and build a bridge to reach ultimate utility.

In the medical realm, "Bench to bedside" is a form of implementation strategy that involves the synthesis of knowledge learned at the bench with the ultimate delivery to the patient's bedside. The expression has more recently evolved into the more all-encompassing "Translational Research" guise, which considers that the "bedside" is not always literal. It is important to note that "Bench to Bedside" is a goal of translational research, but should not define it. If interpreted as a unidirectional streamlining of bench to patient, policies to speed up the process of clinicians interpreting research papers would not target the fundamental problem of the research not lending itself to easy translation in the first place. Translational research must describe the iterative process of basic science discoveries being integrated into clinical applications as well as clinical needs and observations driving the focus of basic science. The collaboration and

integration of scientists with clinicians, as well as the integration of academia, healthcare, and industry is fundamental to the translation of scientific discoveries into clinically relevant guidelines.

The translational science spectrum represents multiple stages of research along the path of implementation, from the biological basis of health and disease to interventions that improve the health of individuals and the public, and back again to inspire basic research. The spectrum is not linear or unidirectional; each stage builds upon and informs the others. At all stages, all parties recognize the importance of developing new approaches, demonstrating their usefulness and disseminating the findings. Translation incorporates synthesis of these ideals among invested groups. Keeping the patient's needs in mind is also a critical feature of all stages in translation, for ultimate utility here is the source guiding the efforts of most translational projects.

Modern proponents of a changing healthcare environment are leaning toward an all-encompassing definition of health, in which being healthy involves more than having proper clinical care. Incorporating the patient's needs into every stage of research not only distributes power to the individual, but also helps to keep goals in check for researchers. A large part of translation is the dissemination of knowledge and synthesis of information to span the vast breadth health. Scientists are not in the business of convincing and educating the lay public about the impact of their research findings, though. There are natural barriers inherent in the research a basic scientist conducts. For the basic researcher, it is common that the only time he or she thinks of a patient is as a tactic when appealing to funding institutions. Often, the only time he or she thinks of the larger dissemination of their research projects would be in writing grant applications. How can we as a nation say that this is okay, effectively reducing a sick individual to a means for funding?

From 2003 on, the concept of Translational Research has appeared high on the policy agenda for biomedical research in a growing number of countries. The first TR-initiatives were driven by the desire to finally see effective treatment for an awful disease. Critics assert that medical and societal payoff from many research projects has been suboptimal and slow, especially for some more common illnesses with consistent basic research funding. More recent TR initiatives stem from the observation that health improvements have not kept up with the increased speed of discovery in the life sciences, such as genomics and molecular biology. The completion of the Human Genome Project in 2003 (Mihaescu, 2010) definitely played a role here. Yet rational application of new knowledge into therapies has only minimally materialized as concepts such as personalized and precision medicine, After all, this lavishly funded 'big science'-project did not bring about the promised revolutionary changes in health care or the expected health gains. Recent pleas for TR are thus partly rooted in disappointment about the societal profit from basic research (van der Laan, 2012).

Yet these discoveries have absolutely set the stage for great applications to come. The question is not if these wonderful biological insights will be translated into useful drugs and medical devices, but when. Ultimately, questions reflect back to the efficiency of the translational system as a whole. As health is increasingly perceived as a synthesis of many fundamental aspects, Translational Research focused investigations on defining and understanding the principles underlying such synthesis. Given the time and complexity of translating research findings into direct patient care, there is a continued need to promote the concept of translational research among clinicians, basic scientists, biotechnologists, politicians, ethicists, sociologists, and investors and to further improve efficiency of these translational processes.

The Differences Between Basic, Applied, Clinical, and Translational Research

The translational research pipeline is highly dependent on three different forms of research: basic, applied, and clinical. Historically, the basic science that is the foundation for therapeutics is fundamentally separated from the clinical research conducted, though they overlap mechanistically. The separation stems from differences in the parties involved, and is a product of transferring knowledge through different scientific frameworks. These frameworks vary in researchers' priorities, training, policies that must be abided by, funding, the environment of testing, time scales, and the success/failure rates. Though TR intends to synthesize fundamental aspects of research, ingrained differences provide distinct barriers to establishing common goals among different researchers.

It is important to delineate exactly the parties and practices implicated in the process of TR, and accurate descriptions are as follows: basic science in the laboratory seeks fundamental knowledge about physical or biological processes; applied science in the laboratory includes studies directed toward a specific utility; basic science in the clinic seeks fundamental knowledge on human pathophysiology; applied science in the clinic focuses on the development of a medical intervention.

According to NIH, basic research involves scientific exploration that can reveal fundamental mechanisms of biology, disease or behavior (Zerhouni, 2003). These laboratory studies provide the foundation for clinical research. In 1945, the director of the US Office of Scientific Development and Research proposed the establishment of the National Science Foundation (NSF) and made the following distinction of basic research: *"Basic research is performed without thought of practical ends. It results in general knowledge and an understanding of nature and its laws. This general knowledge provides the means of answering a large number of important practical problems, though it may not give a*

complete specific answer to any one of them. The function of applied research is to provide such complete answers" (Rubio, 2010). The NSF definition thus identifies the main objective of basic research as the acquisition of knowledge without the obligation to apply it to practical ends.

Applied research is any research that may possibly be useful for enhancing health or well-being. During this pre-clinical stage of investigation, scientists develop model systems to understand the basis of a disease or disorder and find ways to treat it. Testing is carried out using cell or animal models of disease; samples of human or animal tissues; or computer-assisted simulations of drug, device or diagnostic interactions within living systems. Though the goals of applied research seem to correspond well with translational goals, applied research is fundamentally a branch of basic research in that it lacks the defined effort to take the research to a practical level. For example, an applied research study might analyze longitudinal data that tracks participants' health and social relationships. The researchers would report their findings in an academic journal. But in translational research, the same study should include some "action steps." The researchers would partner with a community and ask for ideas about how their findings might apply there. Together, they would come up with an intervention plan that would also include scientific evaluation of its effectiveness.

Clinical research differs significantly from both basic and applied research, but still plays a role in the translational pipeline. In 1997, the NIH Director's Panel on Clinical Research issued the following 3-part definition of clinical research:

1. "*Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this*

definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies.

2. *Epidemiologic and behavioral studies.*
3. *Outcomes research and health services research."* (Zerhouni, 2005)

Clinical research includes studies to better understand a disease in humans and relate this knowledge to findings in cell or animal models. The goal of many clinical trials is to obtain data to support regulatory approval for an intervention. These efforts include testing and refining new technologies in people, testing interventions for safety and effectiveness in those with or without disease, and behavioral and observational studies. This stage also includes implementation research to evaluate the results of clinical trials and to identify new clinical questions and gaps in care. In the same vain, researchers study health outcomes at the population level to determine the effects of diseases and efforts to prevent, diagnose, and treat them. Findings help guide scientists working to assess the effects of current interventions and to develop new ones.

The NIH's definition of clinical research has been widely accepted by institutions and programs and provides a common basis for NIH-funded clinical research training programs. Providing a clear and concise definition of clinical research has facilitated cross-program efforts to identify core competencies, best practices, and meaningful outcomes that are relevant across the broad spectrum of training in clinical research. This in turn has allowed program evaluators to develop useful assessment metrics to document the success of training programs.

The definition of translational research is less clear than the definitions of basic and clinical research. Although a Medline search indicates that the term translational research appeared as early as 1993, there were relatively few references to this term in

the medical literature during the 1990s, and most references were to research about cancer. At the time, the literature on cancer tended to use the term translational research to refer to work spanning different types of research (e.g., immunology studies spanning basic and clinical research) or work spanning disciplines within a particular type of research (e.g., bench research involving molecular genetics and immunology).

A simple literature search on Translational Research includes over 150,000 results, most littered with attempts in various fields to define the term. Because translational research is not clearly defined, developers of translational research programs are struggling to articulate specific program objectives, delineate the knowledge and skills that trainees are expected to develop, create an appropriate curriculum, and track outcomes to assess whether program objectives and requirements are being met (Fudge, 2016). Ambiguous and multitudinous answers to basic questions regarding translational research means that policy makers are not providing a clear target for institutions and researchers. The vagueness of the definitions may also obscure accountability with regard to assessing whether the rhetoric matches actions.

Academic institutions and universities support and encourage the investigations that provide a basis for downstream clinical application. While the bank of basic research hums along steadily, with publications building on each other at an exponential rate, translation of these discoveries often moves at a much slower and jagged pace. Discussing the significant bottlenecks in the scheme of translation will help to determine effective methods of implementation. The good news is that most of the obstacles to progress are common to most translational investigations, and thus identifiable. The bad news, however, is that these problems are not small obstacles, and are difficult to overcome. In order to understand these problems in full it is important to

examine translational research from multiple perspectives, as well as describing the current institutional state of the field.

Defining the translational gap

The commonly used metaphor of translation suggests that TR deals with at least two domains, and A is translated into B. But what is in need of translation? And into what should it be translated? To phrase it differently, what are the two sides supposed to constitute the gap in need of a bridge? Various papers refer to "bridging a gap" as a goal of translational research, and though a few conceptions are consistent across multiple papers, the translational gap is not as clearly formulated as some bodies like the NIH make it out to be.

One side of the gap is identical in most publications on TR. It is referred to with terms like "new knowledge" (also: "research findings/discoveries/ideas/insights/information") gained from "basic (biomedical) research" (also: "animal studies/in vitro studies/pre-clinical studies") (Bernstein, 2007; Mojica, 2006; Denholm, 2008; Lean, 2008). Although the range of scientific disciplines and research methods supposed to yield such knowledge slightly varies, the general idea remains the same: the knowledge to be translated comes from pre-clinical studies, in which the human body was not yet involved. The variety of interpretations of TR appears when the other side of the translational gap is pointed out. Side 2 is slightly more ambiguous. The different constructions of the gap are described in Table 1, illustrated by a characteristic quote from relevant papers attempting to define the gap.

Table 1: The construction of translational gaps (van der Laan, 2015)

Side 1	Side 2	Example
Results from new knowledge gained from basic scientific research	A) New approaches or methods	"[…] translating understanding into entirely new approaches to therapy" Bernstein, 2007
	B) Knowledge of the human body	"[…] investigations in humans which define the biology of disease" Mojica, 2006
	C) Medical applications	"[…] to translate more quickly the myriad discoveries in biomedical research into more effective applications relevant to human health and disease" Denholm, 2008
	D) Improvement of clinical practice	"[…] to improve the application of scientific discoveries from "the bench" to actual patient care at "the bedside" […]" Fagnan, 2010
	E) Benefit for the individual patient	"[…] translation of […] scientific knowledge into patient benefit […]" Geraghty, 1996
	F) Improvement of public health	"From evidence based medicine to sustainable solutions for public health problems" Lean, 2008

The above shows that the gap TR is supposed to bridge can be constructed in rather narrow as well as quite broad ways. A narrow conception suggests that TR should bridge a gap between basic science and new approaches for pre-clinical work, knowledge of the human body or medical applications on the other. The conceived result of TR is more knowledge, or a new technology. Another approach uses TR to address a much wider gap, between basic science on the one hand and clinical practice or the actual health condition of individuals and populations on the other. In these cases, the gap spans beyond R&D practices, pointing out that innovative knowledge and products are not automatically used once available.

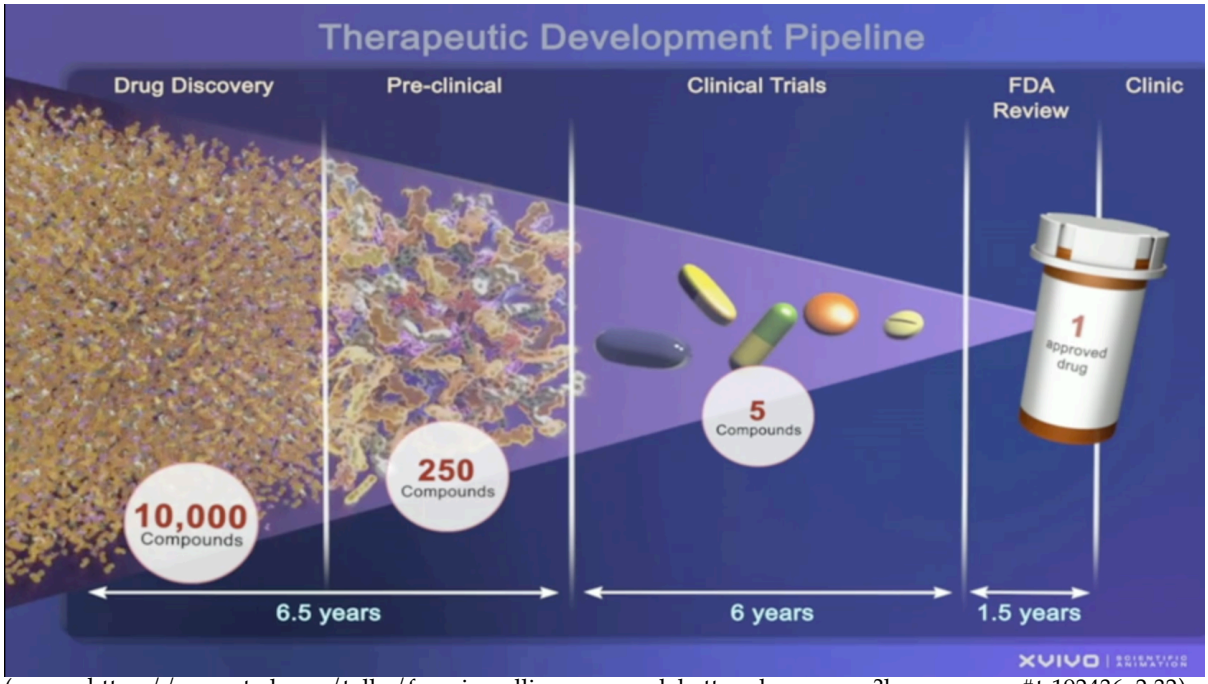
When discussing TR, then, one should be aware that there is not just one translational gap; there are many gaps. Clearly, what TR is supposed to do and aim for depends on the way this gap is constructed. The broader the gap, the more complex TR becomes. In the broader views TR is not just about translating one type of knowledge into another kind of knowledge, as is more or less the case when side 2 is identified with A or B. It can also be about translating knowledge into (better) technologies, practices, bodies (or persons), and social statistics. With each subsequent broadening of the gap, the potential obstacles to translation increase in kind and number, and achieving translation will therefore take more and different types of efforts. Bridging the broad gaps requires that practices and habits have to be reshaped and that roles and responsibilities of various actors have to be changed. Accordingly, a broad construction of the translational gap tends to interpret TR in an extremely comprehensive and ambitious way. The next section explores the current attempts to bridge translational gaps, and identifies the current definitions of common translational practice.

Current models of the translational process

Translational science is a new discipline, so various platforms for education and proliferation have been established by the National Institutes of Health (NIH) to help its many stakeholders and partners accurately conceptualize the translational process, the current roadblocks to its efficient operation, and the opportunities for progress. According to the NIH's definition, translational research is part of a unidirectional continuum in which research findings are moved from the researcher's bench to the patient's bedside and community. Perhaps the most straightforward way to conceptualize this is a therapeutic intervention (drug) developed from a basic mechanistic finding.

To understand the system in place to turn a known molecular mechanism into a pharmaceutical, we must consider what a drug actually is. A drug is a small molecule made up of carbon, oxygen, hydrogen, nitrogen, and other atoms held together in a specific shape. The specific shape of the molecule determines whether in fact that particular drug lands where it's supposed to and acts on the effector as it's supposed to. When developing a treatment for a disease, the scientist needs to find the right shape in a mix of compounds that will ultimately provide the right benefit, safely. As seen in Figure 2 below, the pipeline starts with maybe 10,000 differently shaped compounds that could possibly intervene with the mechanism of interest. The researcher then narrows down the pool through various steps in pre-clinical development to maybe 250 compounds, which then whittles down to 4 or 5 that ultimately get to clinical trial. 14 years after starting the process the researcher maybe gets 1 FDA approval, with clinical costs of over 1 billion dollars for that 1 success (TEDMED, 2011).

Figure 1: The Drug Development Pipeline



(source:https://www.ted.com/talks/francis_collins_we_need_better_drugs_now?language=en#t-192436, 2:32)

A goal of Translational Research is to look at this pipeline as an engineer would and ask how it can be improved, to be faster and more successful. Wouldn't it be nice to be able to test a drug to see if it's effective and safe without having to put patients at risk? How do we know drugs are safe before we give them to people? Are there ways to bypass the time and legal costs of testing each individual compound? Asking and answering these questions is where Translational Research attempts to intervene. But TR itself is not a straightforward process, and involves knowledge transfer along a path of its own.

The most prominent view of translation comprises a linear model that begins with basic science innovations, as illustrated in the figure below. The knowledge that results from basic science is then supposed to be transformed into ideas and knowledge about real affects and in medical technologies that can be implemented in clinical practice. This will ultimately result in healthier individuals and improved public health.

Figure 2: Translational research as a linear process of succeeding steps (Godin, 2006)

Such a linear model of innovation is well-known and ubiquitous in discourse about innovation, both in R&D, science policy making, and economics (Godin, 2006). It has definite advantages, because it orders the different stages of innovation on a timescale and suggests a clear division of labor, thus indicating a seemingly logical way to organize work on future innovation. However, thinking of TR in this linear framework can limit effectiveness. The unidirectional flow of information has been

criticized as inadequate when considering the distinction between basic and applied science and their supposedly temporal, direct relationship (Stokes, 1997). Stokes points out that "use-inspired basic research" had a significant role in the history of biomedical innovation, which is technically outside the typical confines of the linear starting point. This type of scientific research is driven by anticipated use right from the start. He mentions the work of Louis Pasteur, which substantially contributed to both fundamental understandings in microbiology and advances in the treatment of bacterial diseases, as an example of such use-inspired research. Scientific history is also littered with serendipitous findings that completely disregard the typical linear flow of information. In retrospect, innovation may appear to be a linear process, but such a reconstruction disregards that the 'successful' stages in development are not the only possible ones.

The linear model is not only empirically inadequate to describe innovation processes, but may in fact block successful innovation. Several studies show that the division of labor and the timing suggested by the linear model, when used prospectively, limits the abilities of scientists to expand into new territory (Geels, 2000). Lack of attention for implementation, regulatory, or ethical issues during early phases of innovation may cause failure in implementation or dissemination. A unidirectional view on translation neglects that basic science and technology development can learn from and integrate findings from experiments, clinical studies, and even from knowledge from clinical practice and from population studies. This model ignores the benefits of 'backwards translation' (van der Laan, 2015), in that the results from a specific stage of research (like clinical trials) can be 'fed back' to earlier phases of the research process to improve study design and research goals. Views of TR that

conceptualize translation as a linear, unidirectional process thus risk being unfruitful or even counterproductive.

When properly interpreted, the translational research process is highly interactive, with a flow of information in multiple directions. A linear model is not sufficient in accounting for all the opportunities and breaks and information funnels that exist in the process. The concept can instead be thought of as a virtuous cycle. This virtuous cycle is an iterative process that produces new knowledge, biological applications, and medical interventions, involving many different parties interconnected with one another.

Institutional awareness and initiatives

As the world embraces the need for more integrated relationships in healthcare and science, several initiatives have emerged to encourage partnerships. The National Institutes of Health (NIH) has led this charge with the development of the National Center for Translational Sciences (NCATS). With a focus on enabling and encouraging collaborative partnership between clinicians, scientists, and the academia, healthcare, and pharmaceutical industries, NCAT focuses on bringing scientific innovation to the patient community. In 2016, the budget for Clinical and Translational Science Awards (CTSA) was $685.417 million, indicating a substantial commitment toward the translational initiative. The international scientific community has also taken on this initiative. Lifting the barriers around each party and promoting multidisciplinary, inter-institutional, and entrepreneurial collaboration prove to overcome some of the current limitations.

The National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH) was officially established in 2012 to transform the

translational science process so that new treatments and cures for disease can be delivered to patients faster. NCATS, one of 27 Institutes and Centers at NIH, strives to "develop innovations to reduce, remove or bypass costly and time-consuming bottlenecks in the translational research pipeline in an effort to speed the delivery of new drugs, diagnostics and medical devices to patients." NCATS studies translation on a system-wide level as a scientific and operational problem. As a source of institutional support, it strives to develop new approaches, technologies, resources, and models; demonstrate their usefulness in a specific disease or case study; and disseminate the data to the larger scientific community.

Currently, more than 60 medical research institutions in 31 states and the District of Columbia receive funding specifically from the NCATS's Clinical and Translational Science Awards (CTSA) Program. Funding from these awards supports an innovative national network of medical research centers collaborating to improve the clinical and translational research process, in which the following institutions are working together to speed the translation of research discovery into improved patient care:

- About 60 hubs of the Clinical and Translational Science Awards program at Academic Health Centers across the USA
- Translational Research Institute (Australia), Brisbane, Queensland, Australia.
- Translational Genomics Research Institute, Phoenix, Arizona, United States.
- Maine Medical Center in Portland, Maine has a dedicated translational research institute.
- Scripps Research Institute, Florida has a dedicated translational research institute.
- UC Davis Clinical and Translational Science Center, Sacramento, California

Additionally, translational research is now acknowledged by some universities as a dedicated field to study a PhD or graduate certificate in, in a medical context. There are also growing numbers of industry and academic interactions to promote translational science initiatives has been carried out by various global centers such as GlaxoSmithKline and Novartis Institute for Biomedical Research.

As an example of the effectiveness of the CTSA Program awards, investigators and NCATS staff piloted several new initiatives in 2015 aimed at problems limiting translational effectiveness. Such efforts included improving clinical trial recruitment, streamlining the review process for safe conduct of multisite clinical trials, and training and cultivating biomedical researchers skilled in the new field of translational science. These advances in the way clinical studies are conducted will be particularly important to efforts in precision medicine, which will require the ability to efficiently identify, involve and study individuals with specific genetic or other characteristics. Discoveries about the molecular basis of rare diseases is vital, since most have no treatment, but the budget for research on these rare diseases has traditionally been negligible (NCATS, 2015). New scientific insights from genomics and experimental therapeutics show that rare and common diseases often share biochemical pathways and mechanisms, enabling rapid application of the insights gained from the study of one disease to the treatment of others. To this end, efforts of the NIH *Clinical Research Network* brings researchers and patient advocates together to collaborate on studies to understand and treat groups of specific diseases and to share data. Just one of the many results of the novel team-based work of this translational initiative in 2015 was the approval by FDA of sirolimus, which became the first approved treatment for a debilitating and progressive lung disease that strikes women of childbearing age (NCATS, 2015).

Another current effort of the NCATS is their New Therapeutic Uses program, an approach to decrease the time and failure rate of new drug development. The team works to bypass these problems through drug repurposing, a process that enables researchers to find new uses for drugs that already have been approved by the FDA or that have cleared several key steps along the development pathway. As seen in Figure 3, new research efforts can prove extremely useful when aimed at "opening pharmaceutical freezers" (Mullard, 2011) containing drugs that have become obsolete or marginal. Drugs such as these have successfully completed the grueling FDA approval process, and could be an efficient way to find a speedy treatment for a target with similar properties. The process of "teaching old drugs new tricks" has famously resulted in many fast and effective treatments, notably including AZT, a retroviral used for HIV/AIDS that was initially developed as a cancer drug (Mullard, 2011).

Figure 3: Examples of Drug Repurposing through the NIH (NCATS, 2015)

NIH DRUG REPURPOSING

Drug	Initial Indication	Subsequent Indication
AZT	Antineoplastic	HIV/AIDS
Ceftriaxone	Bacterial infection	Amyotrophic lateral sclerosis
Hydroxyurea	Cancers	Sickle cell anemia
Metformin	Type 2 diabetes	Breast cancer
Pioglitazone	Type 2 diabetes	Hepatic steatosis
Raloxifene	Osteoporosis	Breast cancer
Tamoxifen	Breast cancer	Bipolar disorder

NCATS' repurposing efforts resulted in numerous advances in 2015, including the identification of drugs that may treat multiple sclerosis, hepatitis C and Ebola virus

infection (NCATS, 2015). In addition, investigational compounds from pharmaceutical companies are being rapidly developed for new disease indications, including a potential treatment for Alzheimer's disease (Mullard, 2011). These efforts depend on partnerships between academia, the government, the private sector, and patient organizations.

In the real world, the cycle of translation is an exciting, difficult, stop-and-start process comprised of a mix of translational research processes, basic and applied science, and different types of analytic and inventive researchers. The critical question remaining vis-à-vis the virtuous cycle is how can the system be improved?

In June 2005, the Translational Research Working Group (TRWG) was established by the National Cancer Advisory Board (NCAB) to advise the National Cancer Institute (NCI) on the future course of NCI-supported translational research (then dedicated to realizing the promise of molecular oncology for patient and public benefit) (NCI, 2005). The TRWG focused its deliberations on the early translational research portion of translation, which is the research conducted after basic science discovery and before phase III clinical trials. The TRWG thus intentionally did not seek to change any aspect of discovery research. They focused on complementing and extending the initiatives of the Clinical Trials Working Group, which was a separate NCI initiative that concentrated its attention on streamlining clinical trials. Through extensive collaboration, the TRWG accomplished recommendations to restructure fundamental research methods for more effective translation.

Six years later, the Federation of American Societies for Experimental Biology (FASEB) held a symposium hosted by HHMI in Chevy Chase, MD. At this meeting, participants explored the benefits of engaging basic scientists in translational research,

the obstacles that stand in their way, and the roles of research institutions, funders, professional societies, and scientific publishers in helping to overcome these obstacles (Hobin, 2012). Making translational goals a major topic of discussion in these important national meetings not only enhances the value of this kind of collaboration, but allows the problems to be better defined, and goals to be specifically oriented toward their solution.

Many common issues have arisen in the current translational process, and institutions have implemented explicit efforts in response. A major roadblock in the path to developing new therapeutics is the difficulty of accurately predicting whether a potential drug will be safe or effective in humans. New technologies are vital to this process, and through its *Tissue Chip for Drug Screening* program, NCATS supports development of 3-D human "tissue chips" that mimic the structure and function of human organs (NCATS, 2015). In 2015, scientists funded through this program began integrating individual organ chips into multi-organ microfluidic platforms that accurately model the complex functions of the human body. Once fully developed and validated, these systems promise to predict the beneficial and adverse effects of a candidate drug, vaccine or biologic agent more quickly and accurately than the current animal or cell culture models.

Industry has also taken up the challenge of translational research and funded projects independently, or in partnership with various funding bodies or with major academic health centers. These partnerships provide academic researchers with unprecedented access to high-quality clinical and pre-clinical compounds, the building blocks of new drugs, potentially useful for a spectrum of diseases. Such collaborations have the potential to be transformational in stimulating relationships between academia and industry and promoting growth to the pharmaceutical and biotech industry.

Scott Koenig, biotech leader of MacroGenics, called NCATS a "unique opportunity" to fill gaps in drug development that industry is not addressing, and is not incentivized to address (Wadman, 2012). Predictive toxicology, for example, he said, "is not an issue that drug companies would be working on", nor is the identification of biomarkers that won't deliver clinical benefits until years down the line. "This is not something that the drug industry spends a lot of time and money on," he said.

Important translational support elements created over the past few decades include a spectrum of educational programs, conferences, journals, organizations, academic societies, and analytic tools for measuring cost and effectiveness—all parts of a system that nurtures growth of new ideas and ensures the progress of these important goals in science and medicine. For example, scientific journals in Translational Research now include the following: *Science Translational Medicine; Journal of Translational Medicine; Translational Research; American Journal of Translational Research; Translational Medicine* (Omics Online)*; Clinical and Translational Gastroenterology* (Nature); *Clinical and Translational Medicine; Clinical and Translational Science* (Wiley Online).

Though there are many pockets of excellence in the realm of translational research as it is practiced today, there is also much anecdotal and objective evidence to suggest the enterprise is not operating at full speed, due both to inherent challenges in the process and to a set of problems that are self-induced. If we continue to consider translation the responsibility of an outside party or institution that will inevitably be funded by the government, scientists will only continue to move full speed into the discoveries that define their silo, and not give any thought as to the ease of implementation. Similarly, clinical researchers will not even attempt to interpret and apply basic science findings straight from the source without intervention, if it may not seem immediately relevant or feasible.

Fundamental barriers to the translational research process

The most prominent barriers that face translational researchers revolve around the bottleneck step of clinical trials, and include (1) Predicting efficacy and toxicity, (2) De-risking therapeutic development, (3) Clinical research efficiency, (4) Collaboration and partnerships, and (5) Data transparency and release.

(1) Predicting efficacy and toxicity: Predicting biological effects of a drug, chemical, or intervention is one of the most difficult complications to promising basic research results. Foreseeing the consequences of drugs in humans is the purpose of long and grueling clinical trials. Despite promising and costly pre-clinical studies in animal and cell models, 80 percent of candidate drugs fail in human clinical trials because they are found to be unsafe or ineffective. Additionally, more than 30 percent of promising medications have failed in clinical trials because they are found to be actively harmful to human health (Zerhouni, 2005). Because these models often do not adequately represent human biology, they frequently do not accurately reflect how patients will react to an experimental compound. A major area of emphasis in translational programs is the development of model systems for drug and toxicity testing that more closely resemble human physiology (NCATS, 2015). Such advances could save enormous amounts of time and expense by preventing patients from being exposed to potentially harmful or ineffective candidate drugs in clinical studies. In addition, these models have the potential to provide useful information about the basic biology of disease and serve as improved testing platforms for predicting toxicity or other physiological processes as well as evaluating environmental chemicals.

(2) De-risking therapeutic development: Pre-clinical research, which connects basic scientific discoveries with initial testing of therapies in humans, is a failure-prone stage of translation. Innovations in drug discovery and development and management

of development programs can substantially reduce the risks, time delays and costs of advancing basic research breakthroughs into treatments, an approach known as "de-risking" (Lenfant, 2003). Pre-clinical programs are designed both to develop new technologies to make this translational stage more predictive and efficient, and also to de-risk targets and disease projects so that they will be more attractive to potential partners. At this stage it is important for a researcher to work with academic, nonprofit and industry investigators and with patient groups to provide pre-clinical drug development expertise and resources to advance their research and generate data needed for regulatory approval. A researcher must advance potential treatments to the point of attracting external partners who would be interested in investing in completing clinical development, manufacturing and marketing.

(3) Clinical research efficiency: In the clinical stage of the translational process, medications, devices, diagnostic products and other treatment regimens developed in the pre-clinical stage are tested for safety and effectiveness in humans, disseminated to broader patient populations, and studied for their capacity to improve public health. Like those before it, this stage is fraught with scientific uncertainties and operational inefficiencies that limit ability to test new treatments in humans and deliver interventions to patients more quickly.

Clinical trials have underappreciated downsides for investigators if their translational efforts do not lead to positive results. It is critical to remember that all a clinical trial can assess is whether a particular drug, administered in a particular way, is effective in the selected patient population. Unfortunately, a negative or neutral clinical trial result is often interpreted as proof that the mechanistic hypothesis that formed the basis for the trial is incorrect. Although this is true in some instances, clinical trials usually do not provide precise information on disease mechanisms or on the

mechanisms of action of a given therapeutic agent. As most drugs have pleiotropic effects, and as many drugs have off-target effects that can offset their potential benefits, it is not always possible to infer mechanisms of disease from trial results. Thus, negative trial results do not always indicate that the hypothesis supporting the drug use is incorrect. For example, although beta-blockers are now the mainstay of therapy for nearly all patients with heart failure, the early use of beta-blockers for heart failure was attended by worsening heart failure; it took years for investigators to find the right dose of the right beta blocker, the proper timing to initiate therapy and the right patient populations (Mochly-Rosen, 2014).

The failure of a pivotal trial is difficult for researchers, especially if there is a suggestion that patients were harmed because of the treatment. There is also often the impression that negative results of a clinical trial indicate that their field of research is 'dead'. Given how often clinical trials fail and how little clinical trials actually tell us about disease mechanisms, such judgments by the academic community are unfortunate and could impede the development of new ideas. Moreover, when a clinical trial is 'negative' there is often little interest and long delays in publishing the negative results, and crucial elements of the study are often not reported. Many investigators may be bound by confidentiality agreements, and therefore are not at liberty to address the criticisms of their peers.

(4) Collaboration and partnerships: Collaborations among government, academia, industry and nonprofit patient organizations are crucial for successful translation; no one organization can succeed alone. To this end, Translational organizations must lead collaborative approaches in research that span multiple disciplines and are applicable to the broad scientific community. Encouraging partnerships and collaborations across all research sectors including investigators from

NIH, universities and medical centers, other federal agencies, small businesses and industry, and patient groups and advocacy organizations. Patient engagement is also vital for every step of the research process. Incorporating the patient's perspective into the research design by considering their needs or listening to their opinions builds trust and improves the quality of the research. Engagement enables investigators to design studies that measure outcomes of value to patients. This engagement also provides researchers with better access to participants for clinical studies. Among other benefits, a collaborative approach helps maximize public and private resources, expand scientific knowledge, and increase participation in clinical research — all of which help speed the drug development process and get treatments to patients faster.

(5) Data transparency and release: Making data publicly available can spur innovation and scientific discovery that may be difficult to interpret otherwise. Successful translation initiatives must demonstrate and disseminate tools and solutions for use by all translational researchers. Recently many open-source journals and networks have made public dissemination of research findings more direct and transparent, arming the scientific community with translational science resources by enabling the public release of new methods, data and information.

Listed below are some additional challenges that currently plague the translational scheme:

- Insufficient coordination and integration results in a fragmented translational research effort that risks duplication and may miss important opportunities.
- Absence of clearly designated funding and adequate incentives for researchers threatens the perceived importance of translational research.
- Absence of a structured, consistent review and prioritization process tailored to the characteristics and goals of translational research makes it difficult to direct resources to critical needs and opportunities.

- The multidisciplinary nature of translational research and the need to integrate sequential steps in complex developmental pathways warrant dedicated project management resources.
- Translational research core services can be duplicative and inconsistently standardized, with capacity poorly matched to need.
- Inadequate collaboration with industry delays appropriate developmental handoffs.
- Extended negotiation on intellectual property issues delays or prevents potentially productive collaborations.
- Inadequate collaboration with foundations/advocacy groups risks missing important opportunities for patient outreach and integration of translational research efforts.
- The paucity of effective training opportunities limits the supply of experienced translational researchers.

Overcoming such complex barriers to facilitate translation involves a dedicated and deliberate effort by the researchers. Uncovering their personal perspectives on the matter was key in answering a few chief questions: What paths do successes take? Are there commonalities within/across the cases examined, or is each translation unique? Even for successes, are there bottlenecks where discoveries are held up? If so, where? What roles do academia, industry, and institutions play in successful translation? What insights do the case studies suggest regarding the developmental pathways to clinical goals? Twenty case studies spanning the developmental pathways to clinical goals were explored, and the following sections present the specific cases identified in translational successes, the key findings from their analysis, and representative summaries of the common themes examined.

CASE STUDIES

The impact of advanced technologies on translational research is clearly seen in the field of genetics, wherein various recent studies depict clinical efficacy of translational goals in action. For example, some researchers describe the use of genomics to study pathways involved in direct cases of abdominal aortic aneurysm development (Blumberg, 2012) and other diseases, while others discuss the role of genomic analysis for biomarker recognition and public health interventions (Burke, 2010; Michael, 2012). Few social research studies have examined both actions at the bench and the bedside in successful translational cases. Examples of this approach have examined the culture of clinical experimentation in oncology (Lowy, 1997), the nature of arthrosclerosis (Mol, 2002) and pharmacogenetics in the clinic (Hedgecoe, 2004).

This certainly indicates that translation is being pursued intensively by a wide variety of investigators and departments, and in subjects that address areas of either unmet, or indeed, unrealized, clinical need. It is also encouraging to see that most of the papers in this topic come from multidisciplinary groups of clinicians and scientists at various stages of their careers working in close partnership. Collaborations such as these are the driving forces of translational research in terms of bringing together expertise, integrating basic science and clinical applications, and training future generations of clinician-scientists.

Translation of Genetics and Addiction

During the past 10 years, much of the effort to identify genes linked to disease and other conditions of biological interest has focused on genome-wide association studies, in which a set of cases and controls are sampled from a large population and

genotyped, and each mutation identified is evaluated for association with the phenotype of interest. However, more recent work has successfully identified disease-causal genes using whole genome or exome sequencing (Ng, 2010; Roach, 2010). Such studies may prove enormously beneficial for the development of omics-based tests, and indeed such strategies are being used clinically today for the identification of the causal gene mutation resulting in unidentified and uncommon inherited disease states (Michael, 2012).

The newly emerged field of public health genomics has focused on facilitating the translation of genomic discoveries into population-level benefits by applying genetic information to disease prevention efforts, yet the biological, social, and political complexity of human disease has spurred significant challenges. Efforts to translate genetic and other research findings into public health and clinical practice have met significant challenges, and the large-scale problem of addiction has proved a formidable example.

Addiction spans the boundaries between the fields of neuroscience and the psycho-social sciences. Many genes, neurobiological pathways, and socio-environmental factors are implicated in substance-use initiation and dependence. There is no simplistic, linear, cause-and-effect way to describe the etiology of addiction. A multi-disciplinary scientific approach is imperative to understanding the complex social, political, behavioral and genetic interactions that influence its development and is essential to the successful integration of basic research findings, including those from genetic research, into public health and clinical practice. Thus, addiction presents a good case example to examine in the context of translational science. Given the push for translation and its influence on the allocation of funding for basic research, it is also critical for scientists—basic, applied, and clinical—to think about the ways in which

their discoveries might affect public health and society, as well as the ethical and policy issues involved in translation.

The usefulness of genetic information to improve health at a population level is in dispute, as seen in a variety of public forums and exemplified by public debates in the pages of *Science* and the *Journal of the American Medical Association*. Genetic epidemiologist Kathleen Merikangas and statistical geneticist Neil Risch sparked intense discussion among genetic researchers when they argued in *Science* (Dingel, 2012) that there were several diseases, including nicotine addiction, for which traditional public health measures would always be more effective than therapies based on genetic research (Merikanagas, 2003). Others later reiterated this sentiment in the *Journal of the American Medical Association* (Carlsten, 2008). Their viewpoint stands in stark contrast to traditional mindsets of genetic researchers who argue that "employing the power of genetic studies in understanding the underlying biological, behavioral, and environmental factors will enhance research on etiology, treatment, and prevention for these complex diseases" (Berrettini, 2004).

What is the correct approach to integrating genetic information about a complex phenomenon like smoking behavior into traditional population health approaches? Tensions are fueled by the hope and perceived hype of genetic technology for personalized medicine given the promises made, but not yet fulfilled, that the knowledge gained in the Human Genome Project will immediately yield cures for countless diseases and disorders.

When considering the geneticization of addiction, one must view diseases, conditions, and behaviors as being determined all or in part by genetic factors. The controversial nature of addiction as a public health issue renders the etiology and phenotypes of addiction for analysis, and thus incorporating the views of addiction

patients and scientists is imperative to understand the proper ways to treat it. The scientists are important stakeholders who possess a deep understanding of the technicalities and its potential applications. There is a need for the scientific community to be more engaged in discussions with the public and policy-makers concerning when and if discoveries should be translated.

Ostergren et. al. conducted a valuable study that critically investigated the perspectives of 20 leading scientists involved in addiction research and the role of genetics within their field. Not only did this analysis provide an important and relevant compilation of various research projects focused on a realistic translational goal, but learning firsthand from interview responses provided a platform to synthesize the perspectives of investigators performing studies that easily lend themselves to translation that has been lacking. In the following section, I will describe some of the main findings that were gathered from the interview data, and some of the most themes across many perspectives.

Theme 1: "Of course our research translates"

Over half of the participants in the study conducted by Ostergren et. al. endorsed the view that their work could be translated into clinical or public health practice. Most made strong statements about this translational potential, though frequent use of futuristic language implied a rather long translational pipeline.

The most commonly identified translational route was from basic science research to pharmaceutical intervention. One participant saw his/her research as "very much translationally oriented…at the end of the day I would like to find something that leads to a drug" (Neurologist). While pointing out the limitations of genetic research and pharmaceutical interventions, another participant sought the development of a

"pill" that would "make interventions at the psychological and social level more effective." (Neuroscientist). Another imagined an eventual cure through "rehabilitating circuits" in the body that are not working, emphasizing that this would be a "major step forward to returning the person to society who will no longer be a public health burden" (Neurobiologist).

Several envisioned better prevention through population screening or targeted screening of patients seeking preventive care. One highlighted the potential of neurological markers, presenting a futuristic scenario in which individuals could go in for their annual physical to find out there is "too much CRF in [their] amygdala…" which would indicate that they were "…probably under a great deal of stress and may be vulnerable to alcoholism." (Neurobiologist). Another scientist outlined a population-based strategy for preventing addiction including the capacity of "identifying populations at risk and targeting prevention to those individuals… [a] sort of joint assessment of genotype and environment." (Behavioral Geneticist). Another hoped that genetic research would lead to new ways of determining individual risk for addiction:

> *"In a futuristic world when every human's genome sequence will be known and stored in their iPhone, we will be able to say, 'okay, you have elevated risk for cocaine addiction by 2.3 fold based on these 30 genes variations in these 30 genes that you possess'… It would be nice if [this knowledge] is used to work with children when they are younger and identify ways in which the vulnerability to get into drug use can be redirected to more healthful activities"* (Neuroscientist).

A few scientists talked about how biological research into the etiology of addiction could be used to educate the public. For example, one noted the importance of basic science knowledge discovered through addiction research for educating the public about the consequences of drug use. This individual said that "from a public

health policy vantage," this information could help to protect young adolescents from exposure to drugs because they will learn about the changes the brain undergoes as a result of using drugs. (Psychobiologist). A scientist pointed out how our understanding of fundamental kinetics actually translates into useful public health education about the dangers of binge drinking.

Almost all interviewees saw biological research on addiction as having broad societal benefits, such as reducing stigma and self-blame and helping addicts to get over the initial stages of denial. A psychobiologist, for example, recognized that genetic analysis "has done wonders in terms of trying to put addiction into the same realm of medicine as other diseases, like diabetes, which are bio-behavioral, or heart conditions." Many believed their research "might remove some of the kind of moralistic view of [addiction]" and were hopeful that it might help to de-criminalize and place addiction more properly in the realm of disease, rather than social transgression.

Theme 2: "Don't forget the value of basic science"

Study participants were also eager to discuss the relevance of basic research to the larger issues in translational research policy. Participants hoped their research would be translated, but acknowledged that translation takes time, that bodies of knowledge are built slowly over many years, and that basic science has value even in the absence of swift translation. Some thought a drug rather than new knowledge is too often assumed to be the desired product of translational science. A scientist noted:

> *"You have to do the science [to] find a drug and that can come from chance, that can come from playing around with different drugs; different animal systems; that can come from genes. …We know a lot of the genes now, and will we ever have anything better than nicotine replacement [besides] increasing the tax of cigarettes? I don't know –*

maybe, maybe not. But I believe that you have to do the science because it is extremely interesting and it might lead to a new achievement, but it is not a given fact that it will." (Molecular Biologist)

This scientist went on to express caution about overselling the rapid translation of genomic research findings to the public, warning that, "you have to do the science and let it unfold" and, "you hope it will lead to something that is clinically relevant, but it really may not… you can't oversell to the public, especially; then your credibility goes down." Another reasoned that while scientific applications can emerge from basic science by chance, translation is never guaranteed:

"If we are really fortunate, we would identify specific biological mechanisms, genetic mechanisms that you could [use to] develop a therapy… but now, because finding these specific mechanisms has been really hard…, it is much harder to say how that work will translate into benefiting for sure the life of any particular person who has an addiction problem. I still think it is important because … over the course of time, as you aggregate information across these research studies, you have a better idea of what to do next and how to get closer to sort of this translational endpoint" (Human Behavioral Geneticist)

One participant commented on the incongruity between his/her actual research objective and how he/she sometimes finds himself/herself framing his/her research. Though this person believed "curing all of these diseases" is a long-term goal, the individual also cautioned: "the reason for doing what we do is to understand how the brain works. And I think that will lead into insights that do allow for treatment, but I think most of the time it doesn't." (Molecular Neurobiologist). The informant went on to argue that the information we accumulate from genetic research is interesting and important in and of itself, regardless of whether it leads to new treatments:

"The way we are sequencing all these genomes right now for addiction, we are learning as collateral information which genes can tolerate mutations without causing apparent problems. And that tells us something about the evolution of our species… I don't know that those are really, really exciting topics to the average person that just wants a pill to treat their problems, but…I wouldn't say they are useless, in fact, I think they are pretty interesting and… are pretty important. But, it is kind of like the argument about telescopes. I mean, do we really need to know what the Hubbell Telescope shows?" (Molecular Neurobiologist)

Though these scientists believe in the fundamental value of basic science, their responses suggest that the emphasis on rapid translation has created an uncomfortable tension for basic researchers, the same tension revisited again and again.

Theme 3: Problems with pushing translation too quickly

Many of the participants in this study had reservations about the increasing emphasis on translational science. One stated that he/she was "all for it, we need to translate…," but also warned "…we can do harm by putting excessive focus on translation," because the value of basic research may be overlooked leading to unfortunate consequences (Neurosceintist). Another warned that in the future NIH may push even harder for translation:

"I think another major thrust of NIH, in general, is going to be translational which is a big word that says not a lot of anything. But it is going to be translational with a more specific aspect to it, which is how can we convert all of this knowledge that we have… into better treatments for addiction. And I think that is coming." (Neurobiologist)

One participant expressed concern that the emphasis on translation may tempt researchers to misrepresent data in order to obtain funding:

> *"It would be nice if… everyone was quite clear about what they were doing and why and how the bridge from one could go to the other rather than people misrepresenting the data as being genuinely potentially translational just because that is what you have to say to get money. And I think that has become a bit of a problem" (*Behavioral Neuroscientist)

A scientist thought the current translational paradigm should place more emphasis on how research questions are asked: "I think this bench to bedside model is wrong. It has to be integrated. You should be designing your experiments with the translation built in" (Molecular Geneticist). Another suggested that the current focus on translation comes from the public perception that NIH-supported basic research has not led to significant improvements:

> *"I think there has been a big focus now on translation because, in general, we haven't done such a great job of making that translation…because of the perceived insufficient progress, there has been an increased attention to translation.*" (Neuroscientist)

Some interviewees felt that the public expects too much of the scientific community, and that technologies may be reaching clinical application too soon: "I'm a little bit worried that there is too much hope and too much emphasis placed on the application of these technologies." (Human Behavioral Geneticist). None of our participants questioned the value of their work to the overall public health goals of improving addiction prevention and treatment over the long term; however, many questioned the usefulness of the push for quick translation and even the term itself.

Scientists' Perspectives: Benefitting from Translation

Another important way to directly consider the complexities and challenges of translational initiatives is to consider the perspectives of research scientists as a narrative of individual experiences, and subsequently connect common struggles to focus efforts on what can be improved in the translational scheme.

The methodology that investigators use to advance their work significantly confounds the definitions of translational research and basic and applied sciences. There is nuance with which their roles influence their perspective and approach to problems that can significantly affect the ease of translation. Consider the analogy of an analyst and inventor. An analyst examines the mechanistic basis of a particular phenomenon, for example, the molecular elements that control bacterial cell growth or the underlying principles of a medical device. Using a reductionist approach, the analyst examines the physical and molecular mechanisms through hypothesis generation, experimental testing, and then validation or revision based on empirical results. Although the process may involve adaptation of a technology to further the objectives of the analysts, the primary focus is on probing and understanding the unknown. The subject matter is highly focused and the analyst knows "a lot about a little"; in fact, he or she knows more about the molecular phenomenon or device than anyone ever, an impressive feat.

In contrast, inventors know "a little about a lot" and their goal is to create something new—to mix, match, and assemble various bits and pieces of what they know into something never before seen—more like an artist than an analyst. For example, instead of examining the molecular mechanism of bacterial growth, inventors may use a blank canvas and their knowledge of bioengineering, optics, cell biology, genomics, and microscopy to create a novel imaging system. This new technology

would reveal insight into DNA conformational states that mediate cell division, an impressive feat of a different sort, one that will open up whole new avenues of investigation for the analysts.

Perspective 1: Michael Dyer

For Michael Dyer, PhD, an HHMI Early Career Scientist and a basic biologist studying retinal development at St. Jude Children's Research Hospital, the realization that the tens of thousands of papers on the genetics of retinoblastoma had not yet affected the way patients with the disease are treated "fundamentally changed the direction of [his] career and the research direction of [his] lab" ("Our Researchers", HHMI) and his struggles exemplified the trouble of taking the challenges of the clinic back to the laboratory.

Dyer first arrived at St. Jude Medical Center as a junior faculty member in 2001, as the head of a basic developmental neurobiology research laboratory. He had previously spent five years studying normal eye development and genetic mutations of the eye in a large medical research center, but had never once met a clinician, patient, or patient's family. Upon joining St. Jude, working in close proximity with clinicians treating retinoblastoma patients allowed Dyer to spend more time around patients in the clinic. Dyer knew that Rb gene mutations cause retinoblastoma, a rare childhood cancer with only 300 cases per year in the United States (Zhang, 2004). But when he asked the clinicians if the tens of thousands of papers available on PubMed on the Rb gene and pathway had any impact on how patients are treated, they replied that they had no impact whatsoever. This surprising response led him to change the direction of his career and the research direction of his laboratory.

To Dyer, the reason these basic research papers had not been translated into new therapies was obvious: there was a lack of good animal models for this disease. Researchers had tried to develop a retinoblastoma model by deleting the Rb gene from the mouse genome, but the manipulation did not cause the mouse to develop retinoblastoma. Unbeknownst to them at the time, another protein, p107, is able to compensate for Rb in the mouse. When both Rb and p107 are deleted from the mouse genome, retinoblastoma develops in about 50 percent of the animals (Zhang, 2004). Using this model, he was able to test different therapeutics against the disease. In doing so, Dyer applied what he learned from his clinical colleagues about the actual course of treatment in patients (i.e., clinical reality) and tested combinations of broad-spectrum systemic 45 chemotherapeutics in a similar manner in his mice. After going through eight different combinations of drugs and comparing them to the current standard of care, Dyer and his colleagues found a combination that seemed to be better than what children currently were receiving (Dyer, 2005). St. Jude started a new five-year clinical trial based on those data. Although going from nothing to a new clinical trial in about 18 months was satisfying, Dyer hoped to do better. He wanted to develop a more targeted chemotherapy that could be delivered locally to the eye and result in fewer side effects.

Searching for a drug target, Dyer's team discovered that patients with retinoblastoma have increased levels of MDMX, which sequesters p53, a tumor suppressor, and leads to cell proliferation and tumor development. MDMX is amplified in 65 percent of patients and epigenetically turned on in the rest (Laurie, 2006). Once determining a target to go after, Dyer and colleagues developed a model in which the MDMX gene was conditionally over expressed in the mice that develop retinoblastoma. This resulted in a much more aggressive disease in these animals—providing a new

model to test chemotherapeutics (Dyer, 2005). Not wanting to rely solely on a genetic model, they also developed a "xenographic" mouse model in which human tumor cells are transplanted to an eye of an immunocompromised mouse. This resulted in virtually 100 percent engraftment with tumors expressing high levels of MDMX. Collaborations with his chemical biology colleagues, who were able to synthesize an MDMX inhibitor, and clinicians, who provided medical information and tumor specimens, enabled Dyer to begin a preclinical trial focused on inhibiting MDMX (Dyer, 2005).

Dyer believes that the process by which basic investigators can translate their discoveries into clinical applications could be emulated at most major medical or academic research centers ("Our Researchers", HHMI). The building blocks important for driving translation, such as strong basic science departments, animal research facilities, pharmacology and pathology departments, and clinical trial support are already in place. He also noted that some translational work can be done with relatively few resources if one acts creatively. He received no support from St. Jude to fund these studies directly. Rather, Dyer built on a one-year pilot grant of $50,000 and cobbled the rest together through other sources.

Dyer's challenges emphasized a culture of institutional separation. Divisions among clinicians and researchers created knowledge gaps that stifled discovery and innovation. His example of overcoming a communication barrier led to novel therapeutics and improved patient outcomes, and provides insight into better practices to improve translation from the ground up. In order to increase collaboration and participation in translational research, it is necessary to emphasize the value of translational research to both basic and clinical scientists, encourage communications between basic and clinical scientists, provide mentorship, and understand the clinical reality of disease progression and therapeutic interventions.

Perspective 2: Daniel Wagner

For Daniel Wagner, PhD, Assistant Professor, Department of Biochemistry and Cell Biology at Rice University, collaboration was also crucial in filling knowledge gaps that led to ultimate medical utility of a repurposed physical device. A basic developmental biologist working in zebrafish, Wagner embarked on a collaborative project with a physicist after encountering him reading one of Wagner's posters in the hallway (Hobin, 2012). The physicist, Dimitri Lapotko, PhD, was working on a theranostic (therapeutic-diagnostic) application for plasmonic nanobubbles, in which gold particles generate transient vapor bubbles after excitation by short laser pulses (Lapotko, 2011). The biologist and the physicist joined up to test the concept that these nanobubbles could be used to identify cells based on their expression of specific cell surface molecules and to destroy specific cells in a zebrafish (Lukianova-Hleb, 2012). The team used these nanobubbles targeted to the EGF receptor and was able to destroy prostate cancer cells within a host embryo. This was the first step (proof of principle) that the method can be used in vivo as a potential diagnostic tool and ultimately for targeted therapy.

> *"As I saw the group that was being assembled around this plasmonic nanobubble project, I really began to think that there were some serious benefits for me, as a basic scientist, and the potential to move this technology forward and ultimately translate it into the clinic"* (Hobin, 2012)

Among the benefits he cited were participation in a quickly moving multi-investigator project that produced novel results; exposure to new fields and methods leading to new projects; and rapid publication rate. The collaboration has resulted in over 2000 publications regarding the gold nanoparticle theranostic technique since its first publication by the team in 2011.

Perspective 3: Daria Mochly-Rosen

In some cases, differences in culture and mindset can make the translational scientist his or her own best ally. Daria Mochly-Rosen, PhD, Professor and Senior Associate Dean for Research and Founder of SPARK, Stanford University's Translational Research Program, is a protein chemist conducting translational research. Early in her career, she designed rational inhibitors that could turn off heart cell enzymes one at a time and discovered enzymes that could change the rate at which heart cells beat in culture ("Daria…" 2013). She thought this was an important finding that would be of interest to the heart research community, but when she presented her work at a scientific meeting, she found the audience to be disinterested in heart rate regulation. Clinicians, she had been told, already had ways of managing heart rate; they were concerned with problems such as cardiac ischemia (Mann, 2013).

When she brought her idea directly to industry, company after company turned her away. There were good reasons for this: while her work was attractive from a basic research point of view, the barriers to executing it in patients were huge, and many steps had to be completed before reaching that goal. Mochly-Rosen reached out to her colleagues for assistance, but rather than finding support, she was discouraged from pursuing this line of inquiry and from working with industry. Translational research, she was told, is not intellectually challenging, worthwhile, or good for her career. "Career progress in academia is measured by how many papers are published and how much grant funding is received rather than, for example, attempting to produce a new drug," she said (TEDMED, 2015).

Following the advice of a colleague, she invited into her laboratory a physician who wanted to learn basic research and from whom she could learn how to study more

clinically relevant problems. Her work eventually led to the discovery of an inhibitor that when administered after a heart attack dramatically reduces heart damage by 70 percent and prevents subsequent heart failure, a finding that was demonstrated in mice, rats, guinea pigs, rabbits, and pigs. Patents were written and the results published. Yet no one was interested in her findings. Why didn't companies find this useful in patients?

Mochly-Rosen persevered, leaving academia to form her own company, KAI Pharmaceuticals. She spent a year as its Chief Scientific Officer, successfully launching a clinical trial from her groundbreaking discoveries that have since resulted in multiple cardiovascular therapeutics. She went on to share her experiences and founded The SPARK Program at Stanford in 2006. Challenging the academic dogma of how scientific discoveries should reach the pharmaceutical industry, the SPARK model has been implemented internationally and resulted in a cutting-edge book about academic drug development (A Practical Guide to Drug Development in Academia: The SPARK Approach, 2014). Her efforts have helped academics worldwide navigate the so-called "valley of death" between drug discovery and development.

The entire process of development was humbling, but gratifying for Mochly-Rosen. She works to implement infrastructure to enhance the power of one researcher's discovery and will.

> "*Unlike my training in academia, where questions led to the research, in industry I learned to think about the final product and work backwards, to identify what research needs to support such a product... There is nothing more rewarding than [treating] the first patient…or when the trial is finished, looking at the data. It's really a true manifestation of what basic research should eventually lead to*" (TEDMED, 2015).

THEMES

Barrier of culture and collaboration: the Silo problem

> *"There has been, always, a little bit of a mistrust from my end [as] the basic scientist. I always felt that clinical research was either not rigorous enough or boring. And my clinician friends always felt that basic research was not really useful to them when they would see, maybe, the outcome of it in their practice 10, 20, or 30 years later—if they're lucky."*
>
> — F. Nina Papavasiliou, The Rockefeller University

Over time, and as depicted by the many interviews and literature reviews included here, two cultures have evolved in the translational landscape which have proven to be the most significant barrier to the efficacy of translational proceedings: the preclinical and clinical researcher. Researchers can differ greatly based on their perspective and backgrounds, and subsequently the cultures of preclinical work and clinical work differ in intent and general investigative drive. Most basic scientists will rarely step foot in hospitals while few physicians carry out any wet lab work past undergraduate or medical school, well before they have gained a true understanding of clinical needs. How hypotheses are generated, how they are tested, and how they are abandoned vary greatly between the two.

Cultural differences between basic scientists and clinicians include perceived differences that inhibit collaborations between the two groups and discourage basic investigators from pursuing translational projects. Basic scientists see their controlled, hypothesis-driven research as more rigorous than the goal-directed or descriptive research conducted with humans in clinical research settings. Also, clinical researchers may view their work as superior since it has greater relevance to human health and

disease. Noting that she comes from a family of clinical physicians, Dr. Papavasiliou, Associate Professor and head of the Laboratory for Lymphocyte Biology at The Rockefeller University, stated the preceding quote illustrating the different views that persist in the cultures of research and medicine (Hobin, 2012).

As the landscape of healthcare and reimbursement evolves, clinicians will continue to be seen as the social effectors of research work done in a different context, with little to no incentive to spend any additional time pursuing innovative collaborative relationships in science. This has lead to a deficiency in the development of clinician-scientists and translational science collaboration.

There is an obvious lack of communication and collaboration among researchers in different fields, deriving from substantial differences in education, training, and experience. "MDs interested in laboratory-based research face competing demands imposed by patient-care responsibilities. PhDs interested in clinical research face competing demands for projects with shorter turnaround times to publish manuscripts and to compete for grants. MD–PhDs face both sets of competing demands. In addition, it is difficult for PhD scientists to identify ways to work with clinicians and for physicians without a laboratory to find a basic researcher to coinvestigate a clinical question" (Kong, 2010).

When one asks investigators about challenges in translating new research advances into applications, the most frequent complaint is the difficulty in traversing the various components of the system, disciplines and sub-disciplines in academia, the laboratory, the clinic, and the public and private sectors, the so-called silo problem. Certainly, there are many positive aspects emanating from scientific and medical subcultures. However, when the biological or clinical problem at hand requires a

multidisciplinary approach or requires the synergy of more than one discipline, the translational system begins to show its weakness.

An organization or department populated by researchers from within a scientific or medical discipline provides a comfortable group with whom to discuss ideas, share excitement about new advances, obtain technical advice, and commiserate together when projects go badly. Moreover, congregation of like-minded investigators around a focused mission helps to promote productive specialization and a high degree of expertise in many fields, a process essential in moving science and business forward.

In contrast, congregation of unlike-minded investigators from across disciplines stretches everyone's understanding of science and medicine, provides different sorts of thinking and problem solving skills, and exposes investigators to materials and technological capabilities of which they were unaware. Such arrangements also promote work "at the edges," areas where subtypes of science and medicine overlap, a historically difficult yet exciting and often productive cauldron. Moreover, this environment provides ready access to theoretical and technical feedback, offering early-stage reality checks on ideas that transcend an individual's expertise

The former is more usual, though both organizational structures have value. Institutional environments need to be questioned more deeply. Is it better to create a new university or company department organized around a particular theme or discipline, physiology or cancer biology for example? Or is it better to build multidisciplinary departments and units—a biochemist, a physicist, a clinician, an engineer, a social worker, and a business expert? Would this be a more productive arrangement than a theme-centric department or division in academia or industry? Would this approach spin ideas more rapidly and efficiently through the iterative virtuous cycle, with input coming from multiple perspectives?

One does see examples across the research community showing progress in this regard, at least to some extent. The establishment of Clinical and Translational Research Centers at institutions across the US represents recognition of the need for multidisciplinary environments that support the scientific activities and career development of translational researchers. However, these resources are typically provided atop a well-established silo system, as an attempt to counteract compartmentalization, so impact is somewhat limited.

Many myths and misconceptions that plague both parties may only be tackled at the personal level. Some of these myths include that research has no place in a clinician's training; that there is no place for basic research in the clinical training scheme; that every surgical trainee should do some basic research; and that clinicians should only engage in clinical research. These myths need to be tackled at faculty, institutional, and national levels, but requires a fundamental paradigm shift in the way scientists approach their training and their field.

Similarly, scientists come from different backgrounds, and though their methods and language might be literally shared, their intent, approaches, and goals differ significantly. Their projects would thus benefit from a mode of translation to ensure important findings don't get lost or ignored just because they weren't presented to the right person at the right time in the right way. It is common for most scientists to ignore the problem and get stuck further in their own silo, making it necessary for organizations to help establish collaborative goals. Organizations should not simply funnel more money into the same schemes of basic research or applied research or medicine and expect the communication problems to solve themselves. Rather, we must fundamentally change the way researchers think and approach issues, and provide training and funding specifically to overcome the silos.

Barrier of funding and infrastructure

Translational research conducted in academic health centers is confounded by the organizational structure in which the work is performed. Investigators must obtain research funding and appropriate recognition as a part of a research team in a not-for-profit environment which has more readily rewarded basic work, and individual accomplishments. What results is a unique form of conflict of interest, best understood by relating the basic principles underlying the not-for-profit form to the conduct of translational research in the setting of an academic health center.

The "misalignments" described here derive from genuine uncertainties about the best approaches to meeting the research mission in academic health centers (AHC). They also emanate from a reward system in AHC (and more broadly in universities) which recognizes and rewards individual accomplishments more than group performance. These conflicts are not necessarily unhealthy, and can be described as balancing of competing priorities. New initiatives outlined in the NIH Roadmap favor funding for programmatic, team-based research. Concurrently, AHC must configure the reward system to appropriately and accurately value contributions of team members. Doing so will minimize conflict of interest, and will allow AHC to more faithfully meet their mission.

Other Barriers

Various other barriers slow the progress of TR initiatives and exacerbate the barriers listed above. These include: lack of resources, in the form of trained interdisciplinary staff to support investigations; lack of protected time for clinicians to engage in research projects; lack of access to shared resources and knowledge transfer; poorly defined

research-based career paths for clinicians; and a vibrant culture of clinicians valuing clinical care over research, and researchers valuing publication merit over clinical translation.

Trouble with current institutions

Today, most academic research environments are effective in establishing structures to support investigator-initiated basic research efforts, producing an extremely wide array of small laboratories. These labs operate in an open and free environment with a laissez-faire philosophy towards science. If you can fund it, you can do it. The researchers pursue their creative ideas and work in whatever fashion they choose. In some ways, one can consider them to be "academic entrepreneurs," quintessential small business stewards of a sort.

In contrast, these institutions are generally not as good in supporting the applied science phase of translation, due in part to the separationist culture of basic and clinical scientists, as well as a tendency to assert control at this stage whether it is an academic center, business concern, or government entity. Specific manifestations include top-down control of licensing and project direction, poorly conceived academic incentive structures that reward basic science achievements (academic publications) over applied science successes (allowed patents or license agreements), and an over-focus on short-term institutional goals rather than fostering the long-term unbridled creativity and ingenuity of investigators. Like the internal cultural restraints on applied science and commercialization that exist in academia—that it is someone else's problem—institutions frequently displace or minimize the role of creators in the translational process based on external rules and regulations.

WHERE TO GO FROM HERE

Initiatives to encourage scientist collaboration

Get basic scientists to participate/collaborate with translational goals. This would enable them to understand human health and disease and public health which can be a source of intellectual inspiration and stimulation. Would provide opportunities to develop and learn new methods, faster publication rates, promote collaboration that can ignite shared passion, provide new exposure, generate new ideas, provide mentoring opportunities for clinical colleagues, and give them more freedoms.

Given the complexities, risk, and difficulties of translating knowledge into public benefit, perhaps it should be the investigators who are central decision-makers guiding this second stage of translation, the applied phase. They are the ones who discovered or invented the "something new." They are the ones who will walk through walls to make things happen when given a chance, encouraged, and not encumbered by artificial cultural limitations or institutional policy. They are the ones who will take risks that nobody else will consider. They are the ones who will go full steam ahead when other scientists, technology transfer offices, corporate leaders, investors, and business folks all consider success unlikely and their ideas maybe even a little daft. And they are the ones who are ideally positioned to integrate the basic science and applied science silos, short-term and long-term. Their role in the process is essential, yet they are often only minimally involved in translation.

It is not that the inventors and discovers need to do everything hands-on—they do not need to govern or micromanage every project or commercial spinoff. What they do need to do, however, is direct the overall effort and strategy. They need to survey

the laboratory, commercial, and healthcare landscape and assess what needs to be done with their finding, committing to making things happen for the benefit of themselves, their organization, and society. They are the key holders of the creative juice and technical know-how, the intellectual drivers of the inquiry and its potential applications, and should be highly involved in the process, not relegated to the sidelines.

Looking ahead, it likely will be beneficial to more fully empower the creators—the discoverers and inventors. To enable this change, however, institutional power will need to be distributed and dispersed, from administrators and managers to the creative agents. Unfortunately, such a transfer of power is antithetical to most university, government, and corporate leaders, whose goal is usually to amass and then preserve power at all costs, including accepting a loss of translational efficiency to maintain control.

Competition and stratification

The challenge for all those involved (government, charitable, philanthropic, and private funders, biotech industry, pharmaceutical industry, academia, and patient groups) is to identify those opportunities with the greatest potential to provide patient and societal benefit and align their resources to achieve maximal and rapid impact. To meet this challenge, the nation must explore the best ways to optimize the processes by which academia and industry work together to solve such fundamental scientific and medical problems in the process of making new medicines. The best processes likely involve a combination of cooperation and competition. Pharmaceutical rivals are now

cooperating in the early stages of discovery research in precompetitive public–private partnerships (PPPs) to access the expertise of the global biomedical community. Many of these companies are also opening competitions to bring new minds and skillsets to bear on problems in biomedical research via crowdsourcing initiatives. It is a promising prospect that collaborative PPPs and competitive crowdsourcing could improve the process of target discovery and selection, and improvements in this step could accelerate the creation of new medicines for patients.

National Efforts

Open innovation on the national scale is an important way to encourage effective scientific collaboration. Historically, collaborations in the healthcare business between the public and private sectors have been bilateral agreements between one pharmaceutical company and one principal investigator and/or scientific institution. The scientific reputation of the collaborators, their background patent rights, or a recent scientific discovery typically drove the formation of such collaborations. Indeed, such one-to-one partnership models formed the basis for the definition of "open innovation" provided by Henry Chesbrough when he said that companies should use external as well as internal ideas to advance their technology. The term open innovation is now accepted as just one of many terms that capture different but overlapping types of openness during the innovation process. Open initiatives have all been revolutionized by the Internet and the World Wide Web. In the non-networked world, before the Internet, innovation was a centralized, top-down, and difficult-to-scale-up process; in contrast, open innovation in the networked world is increasingly decentralized, bottom-up, and scalable.

In order to access the wider scientific community, the pharmaceutical industry is coming to appreciate the advantages of selective revealing in the same way that the software industry does. Selective revealing refers to a situation in which companies consciously decide to disclose their proprietary information in the expectation that they will receive valuable information in the future.

In response to the notion of increased commercial/industry collaboration among scientists, some would argue that commercialization induces scientific bias due to financial incentives. But what of the other biases that exist in academic incentives? Obtaining grants, being promoted, attaining tenure, publishing manuscripts, and personal recognition are all potential bias-inducing reward mechanisms. Clearly, conflicts of interest across a broad spectrum of activities are simply part and parcel of biomedical research. The remedy is not to shut down the system or abdicate the responsibility of helping patients and the public. Rather, the remedy is transparency, responsible oversight, and well-defined guidelines, features that should be emphasized in all translational organizations, especially when studies touch upon the clinic.

Some national strategies to drive translation could also include efforts from the FDA, in which experts support researchers in regulatory issues and clinical trial design and conduct. Research projects must be designed from the outset in a way that ensures experimental data are gathered to be suitable for use in future submissions to the FDA. This requires expanding the knowledge transfer between academic investigators and the FDA, because both parties share responsibility in the outcomes. There must also be sustained funding dedicated to translational research (build research units that incorporate multidisciplinary groups involving basic scientists, clinicians, bioinformaticians, statisticians, engineers, policy experts), including proper reimbursement for successful collaborations. It is imperative that there are national

forums for collaboration and interdisciplinary discussion, and to highlight the successes and benefits of translational efforts on the national and institutional levels. Otherwise, the scientific community will not be incentivized to personally conduct the collaborative steps that need to be taken. It is also important to increase incentivizing the clinician-investigator track with MD/PhD training and funding. Currently there are about 300 graduates per year in the US. This program could propel translational efforts as it breaks down the cultural barriers, and thus should be emphasized as a priority for funding. Overall, the nation needs to adopt a translation-centered research perspective in order to successfully accelerate translation.

Institutional Efforts: Teaching Translation

University information transfer offices are not set up to implement translational research directly. But, a growing number of universities are creating translational programs that operate beyond the usual technology transfer and aim to teach faculty how to advance the discoveries themselves. Universities with above-average translational track records have instigated such programs. These include Stanford University's SPARK program, the University of California, San Francisco Catalyst program, the Icahn School of Medicine at Mount Sinai's 4D Technology Development program, and now the Dell Medical School's Catalyst program, modeled after its namesake at UCSF (Rosen, 20011).

The programs vary in size and scope but have the common thread of training academics in how to think about their discoveries in the context of a competitive landscape rather than in a strictly scholarly context. Key elements include defining the

unmet need, evaluating the value of an idea versus currently available therapies and investigating the competition.

Appeasing cultural differences is only possible by encouraging collaborative training with lots of overlap. One way to encourage multi-investigator activities is to establish incentive programs that reward these efforts, understanding there is a natural inertia to "leaving the laboratory." There are many ways to accomplish this goal, for example, a royalty-based payment structure, somewhat similar to profit-sharing mechanisms used by many corporate concerns. In this scenario, a defined percentage of commercialization income is dispersed to everyone in a department as a reward for participating in an interactive and collegial environment. In other words, at least to a degree, "your success is my success and vice-versa." If an investigator has a commercial triumph it benefits all, producing income and funds to support infrastructure and training, thereby incentivizing efforts to help colleagues and mentor young researchers—one never knows when and how such efforts will pay off.

The difficulty with this though is that an individual investigator can be either a basic scientist or an applied scientist, but never both—each person must stay in one silo or the other. An ingrained cultural academic credo accompanies this sort of thinking, often proclaimed loudly and in an authoritarian tone; "Everyone knows that basic scientists are highly superior to applied scientists since they are pure, noble, and unencumbered by the grubbiness of commercialization."

What follows naturally is that doing applied science somehow lessens one's ability as a basic researcher and that less knowledge and breadth of experience is preferable to more. A hyperfocus on one's primary scientific interest within a silo is said to be the only way to succeed. Never mind that the actual evidence is contradictory to this assertion, as investigators who are the most entrepreneurial remain productive

with respect to basic science, produce large numbers of high-quality scientific publications, and are often the "superstars" of their fields.

CONCLUSION / OVERVIEW

Summary

Some of the hubbub around translational research has involved looking critically at the healthcare industry's current complex, bureaucratic, authoritarian, regulatory scheme that makes simple goal actualization difficult. But, one can only criticize this structure. It is much more difficult to comment on what can actually be done to improve this scheme, simply because of the vast amount of collaborators and institutional elements involved. Relying solely on one party, such as clinicians, to carry the burden of finding ways to disseminate effective therapeutics of published findings would only further fragment the system with excessive pressure. Clinicians already have the job of interpreting and applying the therapeutics that already exist; adding the extra task of analyzing and testing a new discovery in its relevance to a disease would only exacerbate their struggles.

Similarly, as scientists have the entire biological realm of possibility to discover, asking them to not only discover something new but to also discover how that may affect downstream processes and developments would endanger their personal investment into the very discoveries they set out to explore. So if we can't in good conscience alter the role of clinicians or scientists to take the burden, could we alter the structure of specific clinical institutions to be more amenable to novel findings? It is fair to say that this may create a more disjointed national healthcare system that has been evolving for a century, thus may not be the fastest way to generalized and streamlined implementation of practices. We now are faced with an impasse, with no part of the system amenable to direct alteration to accomplish our necessary and imperative goals of translation. Thus, a more feasible avenue would involve going back to the ground

stage of discovery, in which we incorporate clinical needs from the most fundamental stage of the research process, and to determine a model for research that takes advantage of the collaborative mindset of this new era of medicine.

Concluding remarks

Ultimately, the importance of basic research goes back to what Robert Wilson said to Congress. It has to do with the same reasons that we created the Mona Lisa, painted the Sistine Chapel, built Chartres Cathedral, wrote The Love Song of J. Alfred Prufrock and composed the Goldberg Variations. Da Vinci, Michelangelo, T. S. Eliot and Bach were all trying to find the essence of man's soul and his relationship with the universe and with his fellow men. So were Einstein, Newton, Faraday and Darwin. They were not trying to invent a better mousetrap, but the world did beat a path to their door. Similarly, once our basic understanding of biological systems is firmly in place, translation will willingly follow. The next researcher, when asked to comment on the relevance of his or her basic studies in cell biology to translational research, should echo Wilson: "*It has nothing to do directly with translational research, except to enable it*".

As we rethink the dogma of scientific research around the world, we must embrace the new paradigm of translational research and realize that the journey begins and ends at the bedside. As a health-care community, we must approach our practice honestly to admit and identify shortcomings of our care so that we may turn to applied-scientists or clinician-scientists for solutions to these shortcomings. As a scientific community, we must open our labs to integrated inter-institutional, multidisciplinary collaborations where we acknowledge and reward those undertaking the brave task of

developing solutions, rather than more questions. As administrators, teachers, and mentors, we must continue to invest in the new wave of researchers who may not fit into the traditional paradigm of academic advancement and support the long road of work they have before them. As government agencies, we must continue to build partnerships with the private sector to harness the strengths of all parties. Lastly, as a whole medical community, we must embrace each other with a solitary unifying goal: to act on behalf of patients and provide solutions to their unsolved clinical needs.

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